Claims

1. Use of a heterodimeric fusion in the manufacture of a medicament for treating heart failure with pulmonary hypertension in a subject, wherein an effective amount of the heterodimeric fusion is to be administered to the subject, the heterodimeric fusion comprising:

(i) a first heterodimerisation domain connected to at least one Relaxin A chain polypeptide or a variant thereof; and

(ii) a second heterodimerisation domain connected to at least one Relaxin B chain polypeptide or a variant thereof,

wherein the first heterodimerisation domain heterodimerises with the second heterodimerisation domain, and wherein the heterodimeric fusion has Relaxin activity.

2. The use according to claim 1, wherein the Relaxin A chain polypeptide and the Relaxin B chain polypeptide of the heterodimeric fusion are covalently bound by at least one inter-chain disulphide bond.

3. The use according to claim 1 or 2, wherein the Relaxin A chain and the Relaxin B chain of the heterodimeric fusion are not covalently linked to each other by an amino acid linker.

4. The use according to any one of the preceding claims, wherein the Relaxin A chain of the heterodimeric fusion is a Relaxin-2 A chain and the Relaxin B chain of the heterodimeric fusion is a Relaxin-2 B chain.

5. The use according to any one of the preceding claims, wherein the Relaxin A chain of the heterodimeric fusion is connected to the first heterodimerisation domain via a connector and the Relaxin B chain of the heterodimeric fusion is connected to the second

heterodimerisation domain via a connector, optionally wherein one or preferably both connectors are polypeptides.

6. The use according to claim 5, wherein one or preferably both of the connectors of the heterodimeric fusion have a length of between 6 and 40 amino acids, e.g. one or preferably both connectors have a length of 21 amino acids.

7. The use according to any one of the preceding claims, wherein the first and second heterodimerisation domains of the heterodimeric fusion are derived from an immunoglobulin Fc region ("first Fc region" and "second Fc region", respectively), optionally wherein the first and second Fc regions comprise the constant domains CH2 and CH3.

8. The use according to claim 7, wherein the C-terminus of the first Fc region is connected to the N-terminus of the Relaxin A chain and the C-terminus of the second Fc region is connected to the N-terminus of the Relaxin B chain.

9. The use according to claim 7 or 8, wherein the first and second Fc regions comprise heterodimerisation-promoting amino acid mutations and/or modifications, optionally wherein the heterodimerisation-promoting amino acid mutations are "Fc Knob" and "Fc Hole" mutations, e.g. "Fc Knob" and "Fc Hole" mutations present in the CH3 domains.

10. The use according to any one of claims 7 to 9, wherein the first and second Fc regions are derived from a human IgG1 immunoglobulin.

11. The use according to claim 10, wherein the heterodimerisation-promoting amino acid mutations comprise:

a. "Fc Hole" mutations Y349C, T366S, L368A and Y407V in one CH3 domain; and

b. “Fc Knob” mutations S354C and T366W in the other CH3 domain,

wherein the amino acid numbering is according to the EU index as in Kabat.

12. The use according to claim 11, wherein:

a. the first Fc region comprises the “Fc Knob” mutations and the second Fc region comprises the “Fc Hole” mutations; or

b. the second Fc region comprises the “Fc Knob” mutations and the first Fc region comprises the “Fc Hole” mutations.

13. The use according to any one of claims 10 to 12, wherein the first and/or second Fc region comprises the amino acid mutations L234F, L235E, and P331S, wherein the amino acid numbering is according to the EU index as in Kabat.

14. The use according to any one of claims 4 to 13, wherein the Relaxin-2 A chain polypeptide of the heterodimeric fusion comprises the sequence as set forth in SEQ ID NO: 1 or a variant thereof and the Relaxin-2 B chain polypeptide of the heterodimeric fusion comprises the sequence as set forth in SEQ ID NO: 2 or a variant thereof.

15. The use according to claim 14, wherein the Relaxin-2 A chain polypeptide of the heterodimeric fusion comprises the amino acid mutation K9H, K17M or K17I.

16. The use according to any one of claims 5 to 15, wherein both connectors of the heterodimeric fusion have the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5].

17. Use of a heterodimeric fusion in the manufacture of a medicament for treating heart failure with pulmonary hypertension in a subject, wherein an effective amount of the

heterodimeric fusion is to be administered to the subject, the heterodimeric fusion comprising:

(i) an FcX-con-A fusion polypeptide; and

(ii) an FcY-con-B fusion polypeptide,

wherein:

A is a Relaxin A chain or variant thereof, e.g. a Relaxin-2 A chain or variant thereof;

B is a Relaxin B chain or variant thereof, e.g. Relaxin-2 B chain or variant thereof;

FcY is an Fc region comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and comprises “Fc Hole” amino acid mutations and/or modifications, preferably the amino acid mutations Y349C: T366S:L368A:Y407V;

FcX is an Fc region with “Fc Knob” amino acid mutations and/or modifications, preferably comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and comprises “Fc Knob” amino acid mutations and/or modifications, preferably the amino acid mutations S354C:T366W; and

con is a connector polypeptide, preferably having the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5],

wherein the amino acid numbering is according to the EU index as in Kabat, wherein FcX heterodimerises with FcY, and wherein the heterodimeric fusion has Relaxin activity.

18. The use according to any one of the preceding claims, wherein the heterodimeric fusion comprises a fusion polypeptide with the amino acid sequence of SEQ ID NO: 11 and a fusion polypeptide with the amino acid sequence of SEQ ID NO: 20.

19. The use according to any one of claims 8 to 18, wherein the heterodimeric fusion further comprises one or more Fabs, optionally wherein the heterodimeric fusion comprises one Fab linked to the N-terminus of the first Fc region and a second Fab linked to the N-terminus of the second Fc region.

20. The use according to any one of claims 8 to 19, wherein the heterodimeric fusion further comprises a second Relaxin A chain polypeptide or variant thereof connected to the N-terminus of the first Fc region and a second Relaxin B chain polypeptide or variant thereof connected to the N-terminus of the second Fc region, optionally wherein the second Relaxin A chain is connected to the first Fc region via a connector polypeptide and the second Relaxin B chain is connected to the second Fc region via a connector polypeptide.

21. Use of a heterodimeric fusion in the manufacture of a medicament for treating heart failure with pulmonary hypertension in a subject, an effective amount of the heterodimeric fusion is to be administered to the subject, the heterodimeric fusion comprising:

(i) FcX-B-L-A and FcY, optionally FcY-B-L-A; or

(ii) FcY-B-L-A and FcX, optionally FcX-B-L-A;

wherein:

FcY is an immunoglobulin Fc region with “Fc Hole” amino acid mutations and/or modifications, preferably comprising a CH3 domain having the amino acid mutations Y349C:T366S:L368A:Y407V;

FcX is an immunoglobulin Fc region with “Fc Knob” amino acid mutations and/or modifications, preferably comprising a CH3 domain having the amino acid mutations S354C:T366W;

B is a Relaxin B chain or a variant thereof, e.g. a Relaxin 2 B chain or variant thereof;

A is a Relaxin A chain or a variant thereof, e.g. a Relaxin 2 A chain or variant thereof; and

L is a linker polypeptide, preferably having the amino acid sequence GGGSGGGSGG [SEQ ID NO: 60],

wherein the amino acid numbering is according to the EU index as in Kabat, wherein FcX heterodimerises with FcY, and wherein the heterodimeric fusion has Relaxin activity.

22. The use according to claim 21, wherein the Relaxin B chain of the heterodimeric fusion is connected to FcX and/or FcY via a connector, optionally a connector polypeptide having a length of between 6 and 40 amino acids, e.g. a length of 21 amino acids.

23. The use of any one of the preceding claims, wherein the ratio of Relaxin activity of the heterodimeric fusion over the Relaxin activity of a reference Relaxin protein is between about 0.001 and about 10.

24. The use according to any one of the preceding claims wherein the heart failure is heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction or heart failure with preserved ejection fraction.

25. The use according to any one of the preceding claims wherein the subject has a mean Pulmonary Arterial Pressure of about 25 mmHg or greater, a pulmonary artery wedge pressure (PAWP) greater than 15 mmHg and/or a Right Ventricular Systolic Pressure of about 40 mmHg or greater.

26. The use according to any one of the preceding claims wherein the subject has a Pulmonary Vascular Resistance of less than 3.0 wood units.

27. The use according to any one of claims 1-25 wherein the subject has a Pulmonary Vascular Resistance of 3.0 or more wood units.

28. The use according to any one of the preceding claims wherein the subject has been fitted with a blood pressure monitoring device, preferably a pulmonary artery pressure monitoring device.

29. The use according to claim 28 wherein the pulmonary artery pressure monitoring device is a CardioMEMS pressure monitoring device.

30. The use according to any one of the preceding claims wherein the heterodimeric fusion is to be administered as a pharmaceutical composition comprising the heterodimeric fusion and a pharmaceutically acceptable excipient.

31. The use according to any one of the preceding claims wherein the heterodimeric fusion or pharmaceutical composition is to be administered to the subject by subcutaneous injection.

32. The use according to any one of the preceding claims wherein the heterodimeric fusion or pharmaceutical composition is to be administered by self-administration.

33. The use of any one of the preceding claims, wherein administration of the heterodimeric fusion or pharmaceutical composition results in one or more of:

a) reduced PVR;

(b) reduced mPAP;

(c) reduced ePAD;

(d) increased stroke volume (SV) of the heart;

(e) decreased systemic vascular resistance (SVR) and/or increase estimated glomerular filtration rate (eGFR);

(f) increased ejection fraction; and/or

(g) increased cardiac output;

as compared to baseline levels pre-administration.